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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,079	BEAUDRY ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group VI and the sequence of SEQ ID NO: 1 in the reply filed on August 14, 2006 is acknowledged. The traversal is on the ground(s) that the MPEP 803.04 states that ten sequences normally constitute a reasonable number of sequences for search for examination purposes. Applicants assert that the search of up to 10 polynucleotides would not comprise a serious burden.

This argument has been fully considered but is not persuasive. With respect to claims to nucleic acids, the MPEP states that the requirements of 37 CFR 1.141 have been partially waived to "permit a reasonable number of such nucleotide sequences to be claimed in a single application." The MPEP further states that "**normally** ten sequences constitute a reasonable number for examination purposes and that "**up to 10** independent and distinct nucleotide sequences" (emphasis added) may be examined in a single application. Thereby, the MPEP does not state that 10 nucleotide sequences will be examined in each application. Secondly, while the MPEP addresses the examination of nucleic acids per se, the presently elected claims are not limited to nucleic acids, but rather are drawn to methods for detecting a lung cancer cell. Each of the 8 nucleic acids recited in the amended claims is patentably distinct from one another in that each nucleic acid consists of a different nucleotide sequence and potentially encodes for a protein having a distinct biological function. Further, the claims are not limited to only 8 sequences per se since the claims encompass the detection of any polynucleotide that hybridizes to a polynucleotide comprising the 10 nucleotides of SEQ

ID NO: 1, 2, 6, 9, 13, 21, 25 or 26. The genus of polynucleotides comprising these 10mers is significantly large, and the genus of polynucleotides that would hybridize under any conditions to polynucleotides comprising the stated 10 mers is even larger. Accordingly, it is maintained that a search for methods for detecting the additionally claimed polynucleotides would impose an undue burden to the Office, because the search for methods for detecting polynucleotides comprising the 10 mers of SEQ ID NO: 2, 6, 9, 13, 21, 25 or 26 is not co-extensive with a search for methods for detecting polynucleotides which hybridize with a polynucleotide comprising the 10 mer of SEQ ID NO: 1.

Accordingly, claims 14-18 have been examined herein to the extent that the claims read on the elected invention of SEQ ID NO: 1. Claims 1-13 and 19-29, as well as the subject matter in claims 14-18 of SEQ ID NO: 2, 6, 9, 13, 21, 25 or 26, have been withdrawn from consideration as being drawn to a non-elected invention. In response to this Office action, claims 14-18 should be amended so that the claims are directed to only the elected subject matter.

Claim Objections

3. Claims 15-18 are objected to over the following informalities:

In claims 15 and 16, "obtained by identification of larger fragment" should read "obtained by identification of a larger fragment."

In claim 18, "obtained by identification or larger fragment" should read "obtained by identification of a larger fragment."

In claims 17 and 18, "detection the amplified polynucleotides" should read "detection of the amplified polynucleotides."

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for detecting a lung cancer cell wherein said methods comprise contacting a sample suspected of containing a lung cancer cell with a polynucleotide comprising SEQ ID NO: 1 and detecting hybridization of said polynucleotide with a nucleic acid present in a sample to form a hybridized complement, wherein overexpression of the hybridized complement or the presence of an

amplification product formed using said polynucleotide as a primer is indicative of a lung cancer cell.

The claims define the polynucleotide to be detected as indicative of a lung cancer cell in terms of the fact that it hybridizes under non-specified hybridization conditions to a nucleic acid probe. Thereby, the claims encompass methods in which "low" or "moderate" stringency conditions are employed to perform the hybridization step. As such, the claims encompass the detection of polynucleotides sharing, for example, 30% or 40% or 50% identity with a polynucleotide probe or primer comprising SEQ ID NO: 1 as indicative of a lung cancer cell.

The polynucleotide probe or primer is defined as comprising the 10 nucleotides of SEQ ID NO: 1. The nucleotides flanking these 10 nucleotides of SEQ ID NO: 1 are not defined. Thereby, the overall structural features and biological activities of the probes and primers are not clearly defined by the claims.

The claims also encompass the detection of a lung cancer cell in any organism – e.g., a human, mouse, rabbit, cow, monkey, panda, elephant etc.

The claims recite that the polynucleotide is overexpressed. However, the claims do not recite how overexpression is determined or evaluated – i.e., overexpressed as compared to what?

The claims encompass the detection of any type of lung cancer cell .

Claims 14-17 include the limitation that "the polynucleotide" is located adjacent to a NlaIII restriction site and that there is no NlaIII restriction site further 3' than said site. The claims fail to clearly set forth whether this limitation applies to the polynucleotide

that serves as primer or probe or the polynucleotide which is to be detected. In either case, such a broad limitation defining the location of a sequence, but failing to recite the relevance of such a location with respect to the sequence itself and defining the occurrence of restriction site, but not defining the structure of the polynucleotide probe or primer or polynucleotide to be detected, does not impart a meaningful limitation onto the overall structure or function of any of the polynucleotides encompassed by the claims.

Claims 15, 16 and 18 further include the use of a polynucleotide "obtained by identification of a larger fragment or full-length coding sequences" of a polynucleotide comprising SEQ ID NO: 1. The structure or function of the larger fragment or full-length coding sequence is not defined in the claims.

Thereby, the claims as broadly written, encompass detecting overexpression of any polynucleotide that shares any level of sequence complementarity with any polynucleotide probe that includes the 10 nucleotides of SEQ ID NO: 1. The claims encompass the detection of a significantly large genus of polynucleotides that are not clearly defined in terms of their overall structure or function.

Nature of the Invention

The claims encompass methods for detecting lung cancer by detecting overexpression of a polynucleotide. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches methods of performing SAGE to detect the presence of nucleic acids expressed in lung cancer cells. In particular, the specification teaches that the 10 mer of SEQ ID NO: 1 is expressed in lung cancer cells (see Table I). The specification (page 49) also states that "Table I and II summarize the comparative SAGE analyses of cDNA clones derived from the lung cancers of two individuals and the lungs of two normal individuals."

However, the specification does not provide any data concerning the expression of SEQ ID NO: 1 in other types of normal cells. There is no evidence provided in the specification to indicate that the 10 mer of SEQ ID NO: 1 is exclusively expressed in lung cancer cells. Thereby it has not been established that the presence of or overexpression of polynucleotides comprising the 10 mer of SEQ ID NO: 1 would be diagnostic of the presence of lung cancer cells.

Table 1 indicates that the 10 mer of SEQ ID NO: 1 is present in a carboxylesterase gene having GenBank Accession No.'s X52973 and M5509. However, there is in fact no GenBank Accession No. corresponding to M5509. GenBank does include a listing for accession no. M55509, which consists of the 3' end of a human liver carboxylesterase mRNA. While the specification appears to indicate that the 10mer of SEQ ID NO: 1 may be found in a carboxylesterase gene, there is no evidence of record to indicate that any particular carboxylesterase gene is overexpressed in lung cancer cells as compared to normal lung cells or other types of normal cells.

Thereby, the specification does not teach: (i) overexpression of carboxylesterase nucleic acids in lung cancer cells as compared to normal lung cells; (ii) overexpression of any additional genes comprising the 10 mer of SEQ ID NO: 1 or comprising a sequence sharing any level of sequence identity with SEQ ID NO: 1 in human lung cancer cells; or (iii) overexpression of any gene that includes SEQ ID NO: 1 or any gene that hybridizes to a sequence containing SEQ ID NO: 1 in any non-human organism.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining an association between gene expression levels and the occurrence of lung cancer is highly unpredictable. The art of identifying a gene which is defined in only terms of 10 nucleotides or which is defined as hybridizing to any polynucleotide comprising 10 nucleotides, and then determining an association between the gene and lung cancer is even further unpredictable.

The disclosure in the specification of a 10 fragment which was found to be "overexpressed" in two individuals having non-small cell lung cancer is not sufficient to allow one to conclude that this 10 mer is associated with and can be used to diagnose lung cancer. There is no data to support a conclusion that the findings obtained with these two individuals can be extrapolated to the general population. Expression data obtained with only two individuals would not be considered by those of skill in the art to represent a statistically significant population. Further, the two individuals analyzed consist of a first subject that was 58-years old and had a moderately differentiated cancer at the lower right lobe of the lung and a second subject that was 68-years old and had a poorly differentiated cancer of the lower right lobe (see page 42 of the

specification). The sex and ethnic background of the subjects is not provided. Thereby, it has not been established that expression of the 10 mer fragment is in fact correlated with lung cancer, as opposed to some other factor, such as age, sex, or ethnic background.

It has also not been established that lack of expression of the 10 mer fragment in normal small airway epithelial cells of two independent individuals would serve as an adequate control of the expression level of the 10 mer fragment in normal lung cells. Without information regarding the expression level of this polynucleotide in normal lung cells and normal non-lung cells of individuals having lung cancer, one cannot conclude that "overexpression" of polynucleotides comprising SEQ ID NO: 1 in a sample suspected of containing a lung cancer cell (and containing any additional cell types) could be used to determine the presence of a lung cancer cell.

Also, given the differences in the etiology and pathology of different types of lung cancer, it is highly unpredictable as to whether the results obtained with two individuals having non-small cell lung cancer can be extrapolated to other types of lung cancer.

Regarding the fact that the claims encompass the detection of carboxylesterase gene as indicative of lung cancer, it is highly unpredictable as to whether the results obtained with the 10 mer of SEQ ID NO: 1 can be extrapolated to a carboxylesterase gene. Again, it has not been established that a carboxylesterase gene is overexpressed in lung cancer cells as compared to normal cells. Moreover, the genus of carboxylesterase genes is not limited to the CES1 (monocyte/macrophase serine-esterase I) gene of GenBank Accession No. X52973 or a carboxylesterase gene

comprising the 3' end of GenBank Accession No. M55509. Rather, the family of carboxylesterase genes includes at least 2 other members – carboxylesterase 2 and carboxylesterase 3 – each having a distinct nucleotide sequence and a distinct biological function. While carboxylesterase 2 and carboxylesterase 3 do not appear to include the 10mer of SEQ ID NO: 1, these genes would hybridize to a nucleic acid comprising SEQ ID NO: 1. However, it is has not been established that overexpression of carboxylesterase 2 or carboxylesterase 3 is associated with the occurrence of lung cancer. Each of the carboxylesterase genes also include a substantial number of variants, having mutations that include insertions, deletions and substitutions in carboxylesterase 1, 2 and 3 genes. The specification does not disclose whether it is the wildtype or a particular variant form of a carboxylesterase gene that is postulated to be associated with the occurrence of lung cancer. In the absence of such information, it is highly unpredictable as to whether an association exists between lung cancer and overexpression of variants of carboxylesterase genes or overexpression of wildtype carboxylesterase genes. In the former case, it is also highly unpredictable as to what would be the identity of such a variant.

Additionally, a significantly large genus of known and unknown genes would be expected to include the 10 nucleotide fragment of SEQ ID NO: 1. For instance, the 10 nucleotides of SEQ ID NO: 1 are also present in the human ankyrin 2, neuronal (ANK2), transcript variant 2 (nucleotides 4996-5003 of GenBank Accession No.NM_020977), human prolactin mRNA (nucleotides 811-820 of GenBank Accession No. NM_000948), and human COL9A1 mRNA (nucleotides 561-570 of GenBank Accession No.

NM_001851) Note that each of these genes differ significantly with respect to their full length nucleotide sequence and with respect to the functional activity of the proteins that they encode. However, an association between expression of these genes and the occurrence of cancer is not disclosed in the specification or prior art.

An even larger genus of polynucleotides would be expected to hybridize to a genus of polynucleotides comprising the 10mer of SEQ ID NO: 1. Given that the claims do not specify any conditions of hybridization, such polynucleotides would include nucleic acids having only 20% or 30% etc complementarity with SEQ ID NO: 1. However, it is highly unpredictable as to which, if any, of these polynucleotides would be overexpressed in lung cancer cells as compared to normal cells.

Further, knowledge that expression of a gene may be associated with lung cancer in one organism (i.e., humans) does not allow one to conclude that expression of this gene is also associated with lung cancer in other animals, such as humans, cats, dogs, pandas, elephants etc. In the absence of information regarding the functional properties of a nucleic acid comprising SEQ ID NO: 1 and lung cancer, it is unpredictable as to whether the carboxylesterase gene or other genes will also be present in other mammals and will be expressed at an increased level in other mammals displaying the lung cancer phenotype.

The post-filing date art corroborates the unpredictability of extrapolating the results of gene expression studies performed in one organism to other organisms, such as humans. For example, Coleman (Drug Discovery Today. 2003. 8: 233-235) found that gene expression patterns between mice and humans shared some degree of

similarity, but that the basic patterns of gene expression differed and that there was no general rule for predicting gene expression (page 234). Coleman concluded that '(t)he validity of mouse or other animal species as a human surrogate should not be assumed." These teachings of Coleman support the finding that there is no predictable means for determining whether the gene expression profile obtained in a human will be identical to that in the diverse genus of mammals encompassed by the claims.

The unpredictability in the art is further emphasized by the teachings of Liu et al (Clinical Immunology. 2004. 112: 225-230). Liu studied gene expression in T lymphocytes in human and murine models. Liu (see abstract) reported that "we found very little overlap in the gene expression profile between human autoimmune disease and murine models of autoimmune disease and between different murine autoimmune models." Only 2 out of 129 genes differentially expressed in human SLE were also found to be differentially expressed in animal models of SLE/autoimmune disease (see page 228). Additionally, Liu (page 228) reported that while a conserved gene expression profile was detected in lymphocytes of humans with autoimmune disease, the profile was also seen in unaffected first-degree relatives. These findings of Liu further highlights the unpredictability of using the presence or absence of gene expression profiles to diagnose a disease in the general human population and in non-human mammals.

Amount of Direction or Guidance Provided by the Specification:

Insufficient guidance has been provided in the specification as to how to use polynucleotides comprising SEQ ID NO: 1 to obtain larger fragments or full length

coding sequences that contain SEQ ID NO: 1. While techniques are known in the art for synthesizing DNA, extending DNA, and detecting DNA, knowledge of such general methods does not lead one to specific peptides associated whose expression is associated with lung cancer. Extensive experimentation would be required to identify which nucleic acids in the complete human genome and in the genome of all other organisms contain the 10 mer of SEQ ID NO: 1 and which of this vast number of nucleic acids is associated with the occurrence of lung cancer. The identification of larger length or full length polynucleotides comprising SEQ ID NO: 1 constitutes a research project. Accordingly, it would require undue experimentation to practice the claimed invention because this would necessitate screening the human genome and the genomes of other organisms for the presence of nucleic acids which comprise SEQ ID NO: 1, isolating the larger length or full length molecules, and assaying such molecules to determine whether they encode for proteins which are specifically expressed in lung cancer cells and not expressed in normal cells

The specification also does not provide sufficient guidance to allow one to extrapolate the potential findings regarding human lung cancer to lung cancer in other organisms. The specification does not teach the existence of homologues of SEQ ID NO: 1 in a representative number of other organisms and their association with lung cancer. There is also insufficient information regarding the functional activity of a polynucleotide comprising SEQ ID NO: 1 as it relates to the cause or occurrence of lung cancer to allow one to conclude that any polynucleotide comprising SEQ ID NO: 1 or sharing any level of sequence complementarity with SEQ ID NO: 1 (e.g., 20, 30 40%

complementarity etc) will have a similar functional role in contributing to the development of lung cancer.

While methods for expression profiling are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for genes whose expression may linked to lung cancer. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide any information regarding the criticality of a threshold level of expression which would allow one to conclude that the expression level of a polynucleotide is indicative of lung cancer, particularly within a sample that may contain any cell type in addition to lung cells.

Working Examples

The specification does not provide any working examples in which a lung cancer cell is detected in a human or non-human subject by assaying for any polynucleotide that hybridizes with a polynucleotide that contains the 10 nucleotides of SEQ ID NO: 1.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the

art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has not fulfilled this requirement because the specification has not taught or provided adequate guidance for one to obtain full length or larger length molecules comprising SEQ ID NO: 1 and has not adequately taught one of skill in the art how to detect the presence of a lung cancer cell by detecting a larger length or full length molecule comprising SEQ ID NO: 1 or by detecting any polynucleotide that hybridizes with a nucleic acid comprising SEQ ID NO: 1. Further, Applicants have not provided the novel aspects of the invention since the invention requires the practioner to search for polynucleotides comprising the 10 mer of SEQ ID NO: 1 and then determine which of these currently uncharacterized polynucleotides is associated with the occurrence of lung cancer. Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

5. Claims 14-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to methods for detecting a lung cancer cell wherein said methods comprise contacting a sample suspected of containing a lung cancer cell with a polynucleotide comprising SEQ ID NO: 1 and detecting hybridization of said polynucleotide with a nucleic acid present in a sample to form a hybridized complement, wherein overexpression of the hybridized complement is indicative of a lung cancer cell.

The claims define the polynucleotide to be detected as indicative of a lung cancer cell in terms of the fact that it hybridizes under non-specified hybridization conditions to a nucleic acid probe. Thereby, the claims encompass methods in which "low" or "moderate" stringency conditions are employed to perform the hybridization step. As such, the claims encompass the detection of polynucleotides sharing, for example, 30% or 40% or 50% identity with a polynucleotide probe or primer comprising SEQ ID NO: 1 as indicative of a lung cancer cell.

The polynucleotide probe or primer is defined as comprising the 10 nucleotides of SEQ ID NO: 1. The nucleotides flanking these 10 nucleotides of SEQ ID NO: 1 are not defined. Thereby, the overall structural features and biological activities of the probes and primers are not clearly defined by the claims.

Claims 14-17 include the limitation that "the polynucleotide" is located adjacent to a NlaIII restriction site and that there is no NlaIII restriction site further 3' than said site. The claims fail to clearly set forth whether this limitation applies to the polynucleotide that serves as primer or probe or the polynucleotide which is to be detected. In either case, such a broad limitation defining the location of a sequence, but failing to recite the relevance of such a location with respect to the sequence itself and defining the

occurrence of restriction site, but not defining the structure of the polynucleotide probe or primer or polynucleotide to be detected, does not impart a meaningful limitation onto the overall structure or function of any of the polynucleotides encompassed by the claims.

Claims 15, 16 and 18 further include the use of a polynucleotide "obtained by identification of a larger fragment or full-length coding sequences" of a polynucleotide comprising SEQ ID NO: 1.

Thereby, the claims as broadly written, encompass detecting overexpression of any polynucleotide that shares any level of sequence complementarity with any polynucleotide probe that includes the 10 nucleotides of SEQ ID NO: 1. The claims encompass the detection of a significantly large genus of polynucleotides that are not clearly defined in terms of their overall structure or function.

While isolated nucleic acids consisting of the sequence of SEQ ID NO: 1 meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the claimed genus of polynucleotide sequences "comprising a polynucleotide sequence obtained by identification of larger fragment or full length coding sequences" of SEQ ID NO: 1 or polynucleotides comprising SEQ ID NO: 1 or polynucleotides that hybridize to a polynucleotide comprising SEQ ID NO: 1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, one member of the broadly claimed genus of polynucleotides has been described in terms of its complete structure – i.e., polynucleotides consisting of SEQ ID NO: 1.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, while the specification refers to GenBank Accession No.'s X52973 and M5509 (which apparently should be "M55509"), the specification does not disclose the full length sequences for these genes, the sequence of which would be critical and essential to the practice of the

claimed invention. Further, no such identifying characteristics have been provided for any other polynucleotides that hybridize to a sequence comprising SEQ ID NO: 1 or for larger fragments or full-length polynucleotides that could be identified using SEQ ID NO: 1.

Given the breadth of the claims the genus of polynucleotides that hybridize to a sequence comprising SEQ ID NO: 1 is expected to be substantially large. For instance, the 10 nucleotides of SEQ ID NO: 1 are also present in the human ankyrin 2, neuronal (ANK2), transcript variant 2 (nucleotides 4996-5003 of GenBank Accession No.NM_020977), human prolactin mRNA (nucleotides 811-820 of GenBank Accession No. NM_000948), and human COL9A1 mRNA (nucleotides 561-570 of GenBank Accession No. NM_001851). Note that each of these genes differ significantly with respect to their full length nucleotide sequence and with respect to the functional activity of the proteins that they encode.

Accordingly, knowledge of the sequence of the 10 mer fragment of SEQ ID NO: 1 does not allow the skilled artisan to envision all of the contemplated larger and full-length nucleic acids comprising SEQ ID NO: 1 or polynucleotides that hybridize with a sequence comprising SEQ ID NO: 1. The claimed polynucleotides have not been sufficiently described in terms of their structural properties (length, identity of flanking nucleotide sequences, etc) or functional properties (e.g., activity of the encoded peptide). Thereby, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly

written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the concept of a genus of polynucleotides that are detected or are used as a probe or primer wherein the polynucleotide is located adjacent to a NlaIII restriction site and in which there is no NlaIII restriction site further 3' than said site.

The originally filed specification (page 42) discloses a method in which cDNA obtained from subjects was cleaved with "N1aIII" and used fro SAGE analysis. The specification also teaches that following PCR, PCR products containing two tags ligated tail to tail were excised and cleaved with "N1aIII."

However, this disclosure does not provide support for the distinct concept of a genus of polynucleotides to be used as probes or primer, wherein the polynucleotides are adjacent to a NlaIII site and do not have include a NlaIII site 3' to the NlaIII site. The disclosure in the specification does not address the occurrence of any NlaIII sites within the polynucleotide to be used as a probe or primer or flanking the polynucleotide to be used as a probe or primer. Also, the disclosure in the specification regarding "N1aIII"

restriction sites does not provide basis for the amendment to the claims to recite "NlaIII" restriction sites.

Regarding polynucleotides to be detected, the teachings in the specification do not provide support for the characterization of such polynucleotides as not containing a NlaIII site at any other 3' location of the chromosome or mRNA containing the 10 mer of SEQ ID NO: 1.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-17 are indefinite over the recitation of "is located adjacent to a NlaIII restriction enzyme site, wherein there are no NlaIII restriction sites further 3' than said site" because it is not clear as to what is intended to be meant by this phrase. This phrase is not defined in the specification and there is no art recognized definition for this phrase. The claims define the polynucleotide in terms of the location of NlaIII site. However, since the claims do not define the context of the location of the polynucleotide, it is unclear as to how the location of NlaIII site serves to further define the polynucleotide and it is unclear as to what is meant by a polynucleotide located adjacent to a NlaIII site. For example, it is unclear as to whether the location of the NlaIII site is in reference to the subject's genome, such that the chromosome containing the sequence of SEQ ID NO: 1 does not include a single Nla site at any location 3' of the

NlaIII site that was previously adjacent to the polynucleotide comprising SEQ ID NO: 1. It is also unclear as to whether "said polynucleotide" refers to the polynucleotide comprising a polynucleotide consisting of SEQ ID NO: 1 or the polynucleotide consisting of SEQ ID NO: 1 or to the complementary polynucleotide.

Claims 14-16 are indefinite over the recitation of "overexpression" because this is a relative term, yet the claims do not state what expression is being compared to – i.e., overexpressed as compared to what?

Claims 14-16 are indefinite over the recitation of "hybridized complement." While the claim includes a step of contacting a polynucleotide with a complementary polynucleotide, but does not clearly set forth a step of forming a hybridized complement. Accordingly, it is unclear as to what constitutes the hybridized complement.

Claim 16 is indefinite over the recitation of "the polynucleotide" because it is unclear as to whether "said polynucleotide" refers to the polynucleotide comprising a polynucleotide consisting of SEQ ID NO: 1 or the polynucleotide consisting of SEQ ID NO: 1 or to the complementary polynucleotide.

Claims 17 and 18 are indefinite because the claims recite a step of contacting a polynucleotide with a polynucleotide and then recite a step of amplifying "complementary polynucleotides." However, the claims do not set forth the relationship between the contacting step and the amplifying step. For example, is the polynucleotide that is contacted with the polynucleotide used for amplifying the polynucleotide or is amplification performed using some other unspecified polynucleotide? Also, it is unclear as to what the polynucleotides are complementary to – the polynucleotides that are

isolated from a sample or the polynucleotides consisting of SEQ ID NO: 1 (claim 17) or the polynucleotide obtained by identifying a larger fragment of the polynucleotide of SEQ ID NO: 1 (claim 18). The claims are also indefinite because the phrase "the amplified polynucleotides" lacks proper antecedent basis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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